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Transcranial direct current stimulation unveils covert consciousness

Dear Editor

Thanks to modern neuroimaging techniques it appears that 30% of clinically unresponsive patients (i.e., unresponsive wakefulness syndrome – UWS [1]) retain cerebral functions that are similar to patients in a minimally conscious state – MCS [1], as assessed by fluorodeoxyglucose positron emission tomography (FDG-PET), functional magnetic resonance imaging (fMRI) and electroencephalography (EEG). These patients are newly labeled as MCS* or with cognitive-motor dissociation [2,3]. Even if the majority of them will regain some signs of consciousness, techniques to promote their recovery are still lacking. In this context, transcranial direct current stimulation (tDCS) has been shown to improve the recovery of signs of consciousness in a subset of patients in MCS [4]. This technique offers a safe, inexpensive and easy-to-use tool to stimulate patients' brains in a non-invasive manner. Based on previous studies, the dorsolateral prefrontal cortex (DFPLC) seems to be the most relevant area to target [5].

Here we present the case of a patient who has been repeatedly diagnosed in UWS but who has shown consistent response to commands after 20 minutes of prefrontal tDCS. The patient, a 67-year-old woman who has been considered in a UWS for 3 years and 10 months after a subarachnoid hemorrhage, came to our University Hospital for a week of multimodal evaluation, including daily behavioral assessments with the Coma Recovery Scale-Revised (CRS-R; [6]), resting state fMRI, FDG-PET and EEG, as well as active paradigms. As previously published, the fMRI active paradigm consisted of motor (playing tennis) and spatial navigation imagery (moving though a familiar place) tasks [7], while for the EEG active paradigm, the patient was asked to imagine to move her toes or fingers [8].

The patient also participated in two sessions of tDCS as part of a study protocol, one being active and the other one sham separated by a 48 hour washout period, in a randomized double-blind manner (NCT01673126). The anode was placed over the left DLPFC and the cathode over the right supraorbital region. The stimulation lasted 20 minutes at 2mA. CRS-Rs were performed before and after each stimulation session as previously described in [4].

During all but one of the daily behavioral examinations, the patient was diagnosed as UWS. The only sign of consciousness observed was a localization to noxious stimuli (i.e., the non-stimulated hand made contact with the stimulated hand on two out of four trials). This sign was detected only once during the week of assessment (see supplementary table S1), leading to a final diagnosis of MCS minus (no language related behavior [1]). However, after the active tDCS session, the patient demonstrated reproducible command following at bedside (i.e., close your eyes occurring three out of four trials – diagnosis of MCS plus; i.e., presence of language functions [1]), while no changes were observed after the sham session (see supplementary Table S1). When looking at all CRS-R evaluations, the presence of a reproducible response to command was thus only observed after the active prefrontal tDCS session.

Regarding neuroimaging, the patient presented a preserved brain metabolism in the brainstem and frontal lobes bilaterally, inconsistent with the diagnosis of UWS. Diffusion tensor imaging showed a partial preservation of the white matter, more likely to reflect partial preservation of consciousness. fMRI showed an impairment of the spontaneous brain activity, but active paradigm detected an atypical but reproducible brain activation during the motor task (Fig. 1). Even if atypical, it suggests that voluntary modulation of spontaneous brain activity could be demonstrated. The EEG showed an encephalopathy with a basic rhythm of 5–6 Hz, but the active tasks induced a differentiated response within the motor regions (with a classification accuracy of 70%), suggesting that the patient could understand the task and modulate her brain activity accordingly, as it is usually observed in healthy subjects [8]. Therefore, neuroimaging and neurophysiological data were in line with a diagnosis of MCS plus.

The present report shows the case of a patient who came with the diagnosis of UWS and who was then diagnosed as being in MCS minus following repeated standardized behavioral assessments. Neuroimaging data further suggested that the patient presented preservation of brain activity closer to what is usually observed in healthy subjects (Fig. 1). The presence of a minimal sign of consciousness (i.e., localization to noxious stimuli) was only observed once out of seven behavioral assessments, and active tasks using fMRI and EEG suggested the presence of covert command-following. During this week of assessments, overt response to command was never observed at the patient's bedside. This behavior was solely seen following the experimental procedure of tDCS, after which the patient could reproducibly answer a simple behavioral command. Based on these findings, we hypothesize that tDCS may facilitate motor execution of the command when cognitive functions are preserved in patients with cognitive-motor dissociation [2]. This term is used when a patient does not present any language-related behaviors (i.e., UWS or MCS minus), while (s)he demonstrates command following through modulation of brain activity during active tasks. This category of patients raises ethical questions since their cognitive abilities are better preserved than what can be observed at bedside. In addition, their actual level of cognitive impairment cannot be determined and no reliable communicative tools have been developed yet. In this context, tDCS could be used to trigger behaviors requiring both command integration and motor execution. By increasing cortical excitability of the frontal region, tDCS could unlock some motor execution pathways and facilitate patients' ability to behaviorally interact with their environment. Indeed, the prefrontal region is an area that has been shown on many occasions

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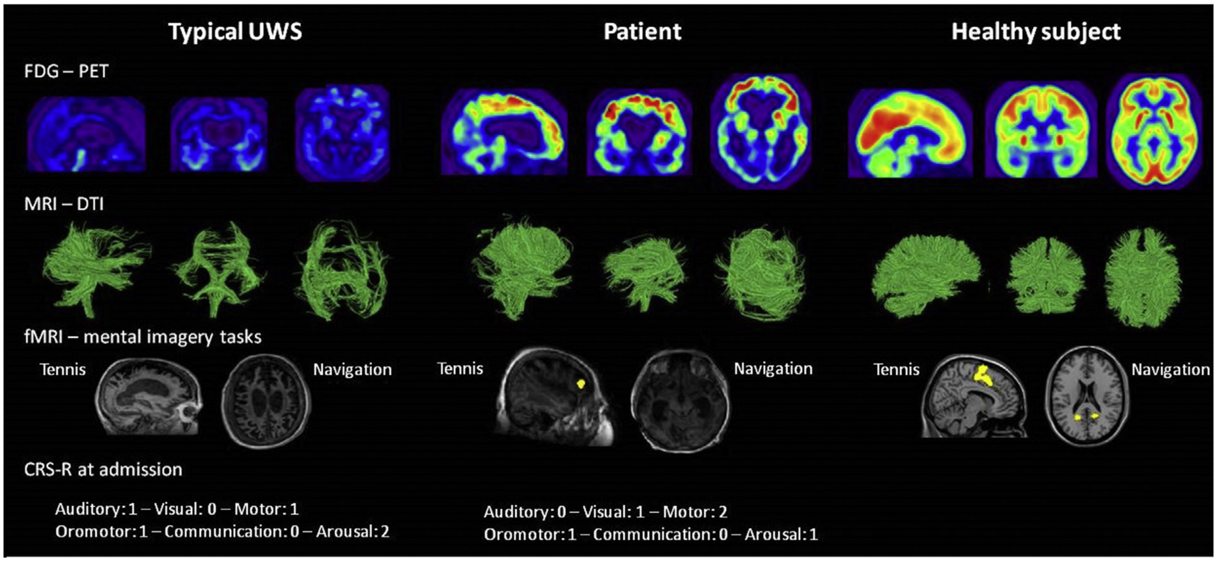

Fig. 1. Neuroimaging and behavioral results of a typical UWS (left, [3]), the patient presented in this case report (center) and a healthy subject (right). The first line represents the fluorodesoxyglucose-positron emission tomography (FDG-PET) results; the second line, the diffusion tensor imaging (DTI) and the third line, the motor and spatial navigation imagery results using functional Magnetic Resonance Imaging (fMRI). The bottom line represents the Coma Recovery Scale-Revised (CRS-R) sub-scores at admission (see supplementary material for more details about the CRS-R).

to be involved in consciousness recovery processes, spontaneous or linked to therapeutic interventions [9].

It should be noted that this patient showed a preservation of brain metabolism in the prefrontal area, which seems to be necessary to clinically respond to tDCS [10]. Future studies on tDCS in patients with disorders of consciousness and documented cognitive-motor dissociation should investigate the residual regional brain metabolism to determine if all tDCS-responders present a preservation of the prefrontal cortex function and if other brain regions could be targeted by this technique. In addition, in the case presented here, the active stimulation was only done once, and the patient never demonstrated a response to command again. Therefore, repeated sessions should be tested to investigate if tDCS could lead to sustainable behavioral improvement.

Conflicts of interest

Nothing to report.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2018.02.002.

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